- minute virus of mice,
- antibodies against adeno-associated virus, the antibody being preferably directed against Cap- and Rep-proteins,

cytomegalovirus, the antibody being preferably directed against glycoprotein B (gpB). --

IN THE CLAIMS:

Please cancel claims 72, 78 and 83-86 without prejudice or disclaimer.

REMARKS

Claims 1-4, 6-18, 23, 25-29, 53, 72, 78 and 83-86 are pending. Claims 5, 19-22, 23, 30-52, 54-71, 73-77, 79-82 were withdrawn from consideration, pursuant to a Restriction of Invention requirement, and subsequently cancelled. Claims 72, 78 and 83 to 86 are herewith cancelled without prejudice or disclaimer. Thus, with entry of this amendment, claims 1-4, 6-18, 23, 25-29, and 53 will be active in this case. Applicants reserve the right to file one or more divisional applications directed to the canceled claims. A marked-up copy of the amendment to the specification, is attached.

I. Information Disclosure Statement

Applicants respectfully request the Examiner's acknowledgment of the Information Disclosure Statement filed August 6, 2001 by forwarding to them an initialed copy of the form 1449 submitted with that Information Disclosure Statement.

II. Rejection under 35 USC § 112

The Examiner rejects claims 1-4, 6-18, 23, 25-29, 53, 72, 78 and 83-86 under 35 USC § 112. The Examiner explains that applicants' previous arguments have been considered but are not found persuasive. Specifically, the Examiner refuses to permit applicants to rely upon teachings in DE 19649645.5 on account of the belief that such teachings are not incorporated by reference.

In response, applicants direct the Examiner's attention to the specification at page 27, lines 17 to 19, where applicants explicitly incorporate by reference all references and patents cited in the specification. In further response, however, applicants herewith amend the specification, pursuant to the Examiner's instructions, so as to add the list of fusogenic peptides disclosed in DE 196 49 645.4 to the specification. In the attached Declaration, Dr. Kontermann, a co-inventor of this application, attests that the inserted

material (Exhibit C, attached to his Declaration) consists of the same material incorporated by reference in DE 196 49 645.4 (See Paragraph 9 of Declaration).

At page 3 of the Office Action, the Examiner discusses applicants' previous reliance upon Nettelbeck for showing the use of the invention's single chain binding molecules as pharmaceutical agents in the treatment of disease. Specifically, the Examiner states that "the specification fails to provide an adequate description for making single chain binding molecules which bind to both a cell surface target molecule and a vector..." and "fails to provide any guidance as to routes and method of administration of vector and single chain binding molecule such that a therapeutic effect on a target cell is observed." Applicants vigorously traverse this rejection. However, solely for purposes of advancing prosecution, applicants herewith cancel claims 72,78 and 83 to 86.

At page 6, the Examiner sets forth a new rejection under 35 USC § 112, first paragraph, of claims 1-4, 6-18, 23, 25-29, 53, 72, 78 and 83-86. Specifically, the Examiner alleges that the specification fails to provide a written description for any VH-VL construct or antibody that binds to any type of vector, viral or plasmid. According to the Examiner, the specification does not identify any particular antibodies which recognize any DNA or RNA plasmid or any viral component, or describe any physical or chemical characteristic of VH or VL nucleic acid or amino acid sequences which

recognize any viral or plasmid vector." (Page 7 of Office Action.) Applicants respectfully traverse this rejection.

In support of this traversal, applicants rely upon the attestations of Dr. Kontermann in the attached Rule 132 Declaration. Dr. Kontermann explains in Paragraph 7 that based upon the teachings in the specification and what was known in the art at the time of the invention, one of ordinary skill in the art could practice the claimed invention. In paragraph 8, he elaborates on this point. Specifically, he carefully examines Example 1 and discusses how the methods described in Example 1 combined with teachings in the art, would permit one of skill in the art to construct other single chain multiple antigen binding molecules, according to the claimed invention, by conventional means. In fact, pursuant to such teachings, Dr. Kontermann did practice the invention and he provides the precise protocol for this in his Declaration. It is clear from this that one of skill in the art would have understood that the inventors were in possession of the invention as of the filing date. The specification both describes and enables the full scope of the claimed invention.

Exhibits D, E, F, G and H are examples of sequences of target cell specific ligands, gene construct-specific ligands and single chain multiple antigen binding molecules constructed from these sequences. The sequences of Exhibit D are the same

ligands disclosed in DE 196 49 645.4, page 3, line 46 through page 9, line 63. This document was incorporated by reference in the specification at page 27, lines 15 to 19. In paragraph 10, Dr. Kontermann attests that the incorporated target cell ligands are the same as those in DE 196 49 645.4. Applicants amend the specification to add the sequences of Exhibit D.

In paragraph 11, Dr. Kontermann states that based on the disclosure of the target cell specific ligands in DE 196 49 645.4, page 3, lines 46 through page 9, line 63, and further based upon the specification of the application and the technical knowledge of one of ordinary skill in the art, such skilled artisan would have been able to identify and construct the VH and/or VL sequences useable as target cell specific ligands as set forth in Exhibit E. Applicants herewith amend the specification to add the target cell specific ligands listed in DE 196 49 645.4.

In paragraph 12, Dr. Kontermann attests that the gene construct-specific ligands listed in Exhibit F and incorporated by reference via DE 196 49 645, listed on page 11, line 55 through page 13, line 40, are the same as the gene construct-specific ligands cited in the application at page 10, lines 10-14. Applicants amend the specification to include these descriptions from DE 196 49 645.4.

In paragraph 13, Dr. Kontermann attests that based upon the disclosure of gene construct-specific ligands disclosed in DE 196 49 645.4, page 11, line 55 through page 13, line 40 and incorporated by reference in the specification, as noted above, and based upon the knowledge in the art, one would have been able to identify and construct the VH and/or VL sequences useable as gene construct-specific ligands. Such sequences are set forth in Exhibit G. In paragraph 14, Dr. Kontermann directs the Examiner's attention to the specification at page 27, lines 1-3 in: *"Examples of antibodies against viral antigens are: anti-HBV, anti-HCV, anti HPV, and anti-HTLV, anti-coxsackievirus or , anti-hantavirus"* and to Example 1. He states that such VH or VL sequences are listed in Exhibit G.

Exhibit H is a set of examples of single chain multiple antigen binding molecules. Such sequences were available to the skilled artisan at the time of the invention.

The Examiner also has alleged that the specification fails to provide an adequate description for making single chain multiple antigen binding molecules which bind to both a cell surface target molecule and a vector. Applicants traverse the rejection and again rely upon Dr. Kontermann's attestations in the attached Rule 132 Declaration. Based upon the teachings in Example 1 of the application, the information incorporated by reference via DE 196 49 645.4 and known teachings in the art at the time of the

invention, one of ordinary skill in the art could by conventional means construct other single chain multiple antigen binding molecules according to the claimed invention, e.g. those which have a specificity for both a plasmid of viral component and a cell surface target molecule. Nettelbeck *et al. Molec. Ther.* 3(6): 882-91 (2001) published by the inventor post-filing supports this assertion. Nettelbeck discloses experiments that were based on the examples in the present specification along with the general knowledge of the skilled artisan as of the application's filing date. This further demonstrates the utility of the single chain multiple antigen binding molecules according to the invention for targeting a vector (adenovirus containing a gene construct) to cells (endothelial cell expressing endoglin CD 105).

CONCLUSION

In view of the above amendment, arguments and attestations of Dr. Kontermann with supporting Exhibits, Applicants submit that the present claims are in condition for allowance, and respectfully request consideration to that effect. Should the Examiner have any questions regarding the present application or believe that further discussion will advance prosecution, the Examiner is invited to contact the undersigned at the number listed below.

Respectfully submitted,

March 11, 2002
Date

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MARKED UP COPY OF AMENDMENT TO SPECIFICATION

Please insert the following at page 10 between the first and second paragraphs:

The following fusogenic peptides disclosed in DE 196 49 645.4, are listed on page 10, lines 30-64:

(1) peptide containing the peptide GLFEALLELLESLWELLLEA (Gottschalk *et al., Gene Ther.* 3: 448 (1996));
(2) peptide containing the peptide AALAEA[LAEA]$_4$LAAAGC (Acm) (Wang *et al., Technol. Advances in Vector Syst. For Gene Ther.,* May 6-7, 1996, Coronado, IBC Conference);
(3) peptide containing the peptide FAGV-VLAGAALGVAAAAQI of the fusion protein of measles-virus (Yeagle *et al., Biochem. Biophys. Acta* 1065, 49 (1991));
(4) peptide containing the peptide GLFGAIAGFIEGGWWGMIDG of the HA2 proteins of Influenza A (Lueneberg *et al., J. Biol. Chem.* 270, 27606 (1995));
(5) peptide containing the peptide GLFGAIAGFIENGWEGMIDG GLFGAIAGFIENGWEGMIDG (Burger *et al., Biochem.* 30, 11173 (1991)) or the peptide GLFGAIAGFIE; ALFGAIAGFIE; LFLGAIAGFIE; LLLGAIAGFIE; LILGAIAGFIE; GIFGAIAGFIE; GLLGAIAGFIE; GLFAAIAGFIE; GLFEAIAGFIE; GLFGAMAGFIE; GLFGAIAGLIE or the peptide GLFGAIAGFIV (Steinhauer *et* al., *J. Virol.* 69, 6643 (1995));
(6) the peptide GLFEAIAEFIEGGWEGLIEG; and
(8) the peptide GLLEALAELLEGGWEGLLEG (Ishiguro *et* al., *Biochem.* 32, 9792 (1993)).

The following target cell specific ligands are disclosed in DE 196 49 545.4 and listed on page 3, lines 46 through page 9,line 63, thereof:

(1) antibody fragments directed against membrane structures of endothelial cells such as, for example, Burrows *et al.* (Pharmac. Ther. 64, 155 (1994), Hughes *et al.* (Cancer Res. 49, 6214 (1989) and Murayama *et al.* (PNAS-USA 87, 5744 (1990))

specially antibodies against VEGF-receptors. (disclosed in DE 196 49 645 Al, p. 5, lines 19-22);

(2) antibodies or antibody fragments directed against membrane structures of immune cells, such as described in Powelson *et al.*, Biotech. Adv. 11, 725 (1993) or antibodies or antibody fragments that bind with their antigen binding part the FC-□, FC-□ or FC-□Rojanasakul et al. Pharm. Res. 11, 1731 (1994), (disclosed in DE 196 49 645 Al, p. 5, lines 50-61);

(3) antibodies or antibody fragments directed against membrane structures of muscle cells, such as the antibody 10F3, antibody against actin, antibody against angiotensin II receptors or antibodies against receptors of growth factors (disclosed in DE 196 49 645 Al, p. 6, lines 48-56);

(4) antibodies or antibody fragments directed against membrane structures of tumor cells, such antibodies are described in Sedlacek *et al.*, Contrib. to Oncol. 32, Karger Publisher, Munich (1998) and Contrib. to Oncol. 43, Karger Publisher, Munich (1992) (disclosed in DE 196 49 645 Al, page 9, lines 50-54).

The gene construct-specific ligands disclosed in DE 196 49 645.4 and listed on page 11, line 55 through page 13, line 40 thereof are:

(1) antibodies directed against epitopes newly introduced into DNA such as antibodies directed against methylated DNA, antibodies against O^6-ethyl deoxyguanosin, antibodies against N^5-methyl-N5-formyl-2,5,6,-triamino-4-hydroxy-pyrimidine,

antibodies against N7-ethyl guanine, antibodies against 0^6-methyl-2'-deoxyguanosine, antibodies against 0^6-ethyl-2'-deoxyguanosine, antibodies against 0^6-N-butyl-2'-deoxyguanosine, antibodies against 0^6-isopropyl-2'-deoxyguanosine, antibodies against 0^4-methyl-2'-deoxyguanosine or antibodies against 0^4-ethyl-2'-deoxyguanosine, antibodies against methylated DNA, especially against N^6-methylated adenin.

(2) antibodies directed against envelope proteins or viruses such as for example

- murine leukemia virus, the antibody being preferably directed against envelope proteins gp70 and p15,
- HIV,
- herpes simplex virus, the antibody being preferably directed against glycoprotein B, glycoprotein H, glycoprotein L,
- cytomegalovirus, the antibody being preferably directed against glycoprotein B (gpB),
- adeno-associated virus,
- minute virus of mice,
- antibodies against adeno-associated virus, the antibody being preferably directed against Cap- and Rep-proteins,

cytomegalovirus, the antibody being preferably directed against glycoprotein B (gpB).